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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,551	09/27/2001	Muthiah Manoharan	ISIS-4847	3873

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,551	MANOHARAN, MUTHIAH	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2004 and 10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30 and 52-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30 and 52-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11 Jan. 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. applicant's submission filed on April 7, 2004 has been entered.

Status of Application/Amendment/Claims

applicant's responses filed April 7, and May 10, 2004 have been considered. Rejections and/or objections not reiterated from the previous office action mailed February 13, 2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claims 28-30 and 52-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated gene inhibition *in vitro*, does not reasonably provide enablement for methods of contacting an organism with a compound of the instant invention wherein said methods embrace treating any animal with any disease associated

with the undesired production of any protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the same reasons of record as cited in the Office action mailed June 5, 2002.

applicants continue to traverse the instant rejection by pointing to positive results from a phase III clinical trial of Genta Inc.'s antisense drug, Genasense. Although applicant has acknowledged that the enablement portion of 35 U.S.C. § 112 first paragraph requires that the invention be enabled as of the instant effective filing date of July 14, 1998, and that Genta announced its Phase III results on 10 September 2003, applicant responds by indicating that these trials were started years earlier, and that the results of the earlier phase I clinical trial of G3139 were published in time to enable the instant invention. The results of said clinical trial, discussed in applicant's exhibits A and B, allegedly indicate one complete response, two minor responses, and nine patients with stable disease as a result of treating patients with an antisense oligo targeted to Bcl-2. Applicants argue that these results establish that patients with non-Hodgkin's lymphoma could be treated with antisense technology on or before 19 April 1997, the publication date a reference describing said results, and that the instant claims are thus enabled.

In response, it is set forth that applicant's reliance upon the data from the Phase I trial is misplaced for several reasons. The primary reason that such data is not considered convincing is because enablement is considered in view of the art as a whole rather than the results from one test, and further, whether such results are considered predictable or unpredictable (see M.P.E.P. § 2163). As discussed in previous actions, it is not argued that there have been several published instances describing the successful use of antisense oligonucleotides to inhibit the expression of

a gene *in vivo*. However, such results are considered to be unpredictable when viewed against the state of the art as a whole. In addition to the numerous reviews cited in previous Office actions, more recent publications indicate that progress has been grudgingly slow. For example, a recent scientific review of the state of the art of nucleic acid therapeutics has been written by Opalinska and Gewirtz (Nature Reviews, 2002. 1:503-514) indicating that "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain...It is a widely held view that molecule delivery, and selection of which messenger RTNA sequence to physically target, are core stumbling blocks that hold up progress in the field." (page 503, 2nd paragraph). They conclude that "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability." Thus, this manuscript published five years after applicant's effective filing date, when combined with the five previously cited review articles indicating similar unpredictability, reinforces the view that the field as a whole remains unpredictable.

Furthermore, it is not clear how the phase I results provided by applicant supports applicant's specific claims of enablement, because the antisense molecules used by Genta are different from those claimed instantly. Even if they were the same, the evidence of one antisense compound in one clinical trial is not commensurate with the scope of the instant methods, which encompass methods of using any and all antisense oligonucleotides with alternating phosphorothioate bonds in the treatment of any and all disease. Finally, applicant points out that only 1 out of 21 demonstrated a complete response, which corresponds to chance (i.e. $p>0.05$).

For all these reasons, one of skill in the art would not have considered the Phase I results presented by applicant to overcome the known and significant unpredictability in the art of using antisense oligonucleotides *in vivo*, and would have understood that to practice the invention now claimed by applicant, even today in 2004, would require undue trial and error experimentation with no reasonable assurance of ever achieving *in vivo* success. The rejection is thus maintained.

Claim Rejections - 35 USC § 112

Claims 28-30 and 52-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a method comprising contacting an organism with an oligonucleotide compound that has been chemically modified.

applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

In this case, applicant's claim language is broadly drawn to *any* method comprising contacting an organism with a modified oligonucleotide. Such language is considered to be extremely broad, encompassing any method of inhibition *in vivo* and further, to treatments of any disease. Applicant has prophetically disclosed the use such oligonucleotides in the treatment of disease, but has exemplified only *in vivo* localization studies in which neither inhibition nor treatment were addressed in any manner.

Furthermore, as documented and emphasized in the rejection under 35 U.S.C. § 112 first paragraph enablement above, the art of *in vivo* inhibition and treatments which rely upon the action of antisense oligonucleotides is considered to be unpredictable. Thus, there is considered to be substantial variation within the genus of any method of administering a modified oligo to an organism, particularly when the specification focuses prophetically upon *in vivo* methods of

inhibition and treatment. Applicant simply has not provided an adequate nexus between the instantly disclosed structures and the unpredictable functions embraced by the instant claim language pertaining to *in vivo* inhibition and treatments. Accordingly, because what constitutes a "representative number" is an inverse function of the skill and knowledge in the art, and because the art of antisense-mediated methods of inhibition and treatment of disease is both large and unpredictable, applicant is not considered to possess adequate written description of the genus of any method embracing any method of inhibition and/or treatment of disease based upon a disclosure which provides only prophetic guidance of structures that have the unpredictable function of achieving *in vivo* inhibition and/or treatment.

No claims are allowed.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD
Patent Examiner, Art Unit 1635